REMARKS

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 2-4, 10 and 11 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. More specifically, claim 2 has been rejected as being in improper Markush format. Applicants respectfully note that under M.P.E.P. §2173.05(h),II, 'alternative expressions using "or" are acceptable.' As such, claim 2, is presented in acceptable format. However, in the interest of facilitating prosecution, Applicants have amended claim 2 to place the claim in more traditional Markush format.

Claim 4 has been rejected for recitation of "a part or parts or the...." Claim 4 has been amended to correct this apparent typographical error and instead recite "a part or parts of the...."

Claim 10 has been rejected for recitation of "The method claim 1...." Claim 10 has been amended, as indicated above, to properly recite, "The method of claim 1...." Claim 10 has been further amended pursuant to the suggestions of the Examiner to clarify the mete and bounds of the claim. Claim 11 has been similarly amended.

Claim 13 is believed to appropriately define the invention, in view of the above-indicated amendments.

As the above amendments to the claims address the rejections of the Examiner and fully define and clarify the claims, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 2 has been rejected under 35 U.S.C. § 112, first paragraph as lacking support for recitation of "nonsense" mutations. "Nonsense" mutations are fully supported by the specification on page 3, lines 13-14, wherein a "nonsense" mutation is defined as one causing truncation of the protein, i.e. the inappropriate creation of a stop codon. "Nonsense" mutations are further supported in the specification by the data of Table 2, wherein mutations creating nonsense mutations in p53 have been shown. See amino acids residues 204, 317, 331 and 342, wherein the respective amino acid residues were replaced with stop codons, thus creating nonsense mutations.

Claims 1-11 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. More specifically, the Examiner maintains that claims encompass the independent use of mutation

and node status in prognosis, for which the specification is not enabled.

Claim 1 has been amended to more clearly define that the results obtained in steps c)(i) and c(ii) are used in combination, i.e. both node status and mutational analysis, to make the prognosis. Applicants believe this amendment fully addresses the issue of enablement raised by the Examiner.

Rejections under 35 U.S.C. § 103

Claims 1-8 remain rejected under 35 U.S.C. § 103, as being obvious over Elledge et al. in view of Callahan and Hartmann et al. In the rejection the Examiner raises the following points.

1) Firstly, the Examiner notes on page 6, of the Final Office Action, that the claims as currently written recite "analyzing the DNA sequence..." rather than "sequencing the DNA." Thus, the use of SSCP is encompassed by the claims.

2) The Examiner asserts that Elledge et al., in fact, sequence samples to determine p53 mutations.

3) On page 7, of the Final Office Action, the Examiner indicates that there is no evidence that DNA sequencing is superior to SSCP due to inefficiency of the SSCP analysis.

4) The Examiner further states that any unexpected advantage must be disclosed at the time of filing.

5) The Examiner asserts Elledge et al. found the combination of p53 mutation and node negative status was a poor prognostic indicator with a higher risk of relapse. Based on this, the Examiner asserts that Elledge et al. teach that p53 mutation combined with node negative status indicate a prognosis of relapse and provide guidance that adjuvant therapy is required.

6) The Examiner maintains that it would be obvious to combine nodal status analysis of Callahan with the mutational analysis of Elledge et al.

Applicants respectfully traverse this rejection and will address each point raised by the Examiner, in turn. Firstly, the Examiner asserts that the claims recite "analyzing the DNA sequence..." thus encompassing the use of SSCP. Claim 1 has been amended, as indicated above, to more clearly recite in steps a) and b) - a) "determining the nucleotide sequence of the complete coding region of the p53 protein; b) analyzing the nucleotide sequence determined in step a) for the presence of mutations." Support for determining the "nucleotide sequence of the complete coding region of p53" is found in the experimental section of the

specification, wherein the complete nucleotide sequence was sequenced. Thus, claim 1 has been amended to more clearly recite that the present invention includes a step of sequencing the samples.

As indicated in point 2) above, the Examiner asserts on 6 of the Final Office Action that, "Elledge et al. does sequence samples to determine p53 mutations...." Page 97, left, 1st paragraph through the right column, 1st paragraph, of Elledge et al. states,

> We focused our search for p53 mutations on exons 5 through 9 because the majority of p53v mutations in tumors have been found in this region (30). This region of the gene is highly conserved in evolution (31), which reflects its functional significance. Three segments of the p53 sequence in this region were amplified by DNA PCR. These segments encompassed exons 5 and 6, exon 7, and exons 8 and 9. The amplified fragments were examined by SSCP analysis...[left column, final paragraph] An example of SSCP analysis for exons 8/9 is seen in Figure 1. Tumor DNA samples were run under both non-denaturing and denaturing conditions. Under denaturing conditions, the DNA is separated into single strands. An abnormally migrating band, representing a mutation, is seen in the far right lane. This abnormal band was cut from the gel, and the DNA cloned and sequenced.

Thus, it is clear from the disclosure of Elledge et al. that the entire p53 region is not sequenced and not all samples were sequenced in any way. The only sequencing that was done was a

limited partial sequence analysis of those mutations, which were identified using SSCP.

On the bottom of page 6, spanning page 7 of the Office Action, the Examiner asserts that there is no evidence that DNA sequencing is superior to SSCP due to inefficiency of the SSCP analysis. (Point 3, above). The degree of mutations detected using SSCP will depend on the conditions used, and on the particular gene being analyzed. For p53, specifically, it is now known that SSCP is inefficient. As evidence of the inefficiency of SSCP in detecting mutations of p53, enclosed herewith is an article by Tolbert et al. wherein it is clearly stated that, "p53 immunoreactivity and single strand conformational polymorphisms analysis often fails to predict p53 mutational status." Mod. Pathol. 12(1) 54-60 (1999). As further stated on page 60 of Tolbert et al. the sensitivity of SSCP for detecting mutations of p53 is as low as 62%. Thus, Applicants have clearly evidenced the inefficiency of SSCP in determining sequence mutations of p53.

In point 4) listed above, the Examiner asserts that any unexpected advantage must be disclosed at the time of filing. Applicants respectfully request that the Examiner explain the basis for this assertion. M.P.E.P. § 716.02(f), citing to In re

Chu, 66 F.3d 292, 298-299, 36 U.S.P.Q.2d 1089, 1094-95 (Fed. Cir. 1995) clearly instructs,

> We have found no cases supporting the position that evidence or arguments traversing a §103 rejection must be contained within the specification. There is no logical support for such a proposition as well, given that obviousness is determined by the totality of the record including, in some instances most significantly, the evidence...proffered during ex parte prosecution.

It was further held in Ex parte Sasajima, 212 U.S.P.Q. 103,104-5 (Bd. Pat. App. and Interfer. 1981), that evidence relating to initially undisclosed relative toxicity of claimed pharmaceutical compounds must be considered. Nowhere is it indicated that an unexpected advantage over a prior art reference must be disclosed at the time of filing. Both the rules and the M.P.E.P are clear in that an Applicant may rely on an unexpected advantage not disclosed in the specification to establish the non-obviousness of an invention.

Previously known methods, such as those of Elledge et al., for using p53 mutational status as a prognostic tool, had the following two prejudices.

a) It was considered that one could disregard mutations outside the conserved region when using p53 as a prognostic marker.

b) It was believed that the determination of p53 mutational analysis could greatly simplified by using methods such as SSCP.

The present inventors have found distinct weaknesses associated with the presumptions (a) and b) above), of the prior art methods and developed an improved prognostic method, which relies on full mutational sequence analysis of p53. The advantages associated with the present method exist independent of whether nodal status is also used, although combining the full p53 sequence analysis with nodal status results in an even more improved prognostic tool. The advantages associated with the full sequencing of the p53 gene are evidenced by the enclosed article by Kressner et al., J. Clin. Oncol. 17(2) 593-599 (1999)(co-authored by the present inventor), wherein it is shown that the relative hazard for a mutation is 1.7, independent of where the mutation occurred. Further shown in Table 3 of the article, the relative hazard for patients with a missense mutation is 1.45 and for other than a missense mutation 2.36. Kressner et al. further teach in Figure 1, that most missense mutations are localized in the central conserved areas. However, most of the mutations which are other than missense are localized to end portions of the gene. See page 597, right column, of Kressner et al. These mutations would have been missed using the SSCP analysis of Elledge et al.

wherein only the conserved region was analyzed. See page 97, left column, of Elledge et al.

Although, the Figures in Kressner et al. regarding the relative hazards, discussed above, do not incorporate nodal status they demonstrate unexpected advantages associated with mutational analysis alone of the complete p53 coding region. Points 5) and 6) above, regarding nodal status, in no way suggest the advantages associated with full p53 sequence analysis. As such, points 5 and 6) do not render the present invention obvious.

In summary, the methods of the prior art, which used p53 mutational analysis as a prognostic tool, were based on two premises, a) mutations outside the conserved region of p53 could be disregarded; and b) p53 mutational analysis could greatly simplified by using methods such as SSCP.

The present invention has unexpected advantages over the prior art because, as evidenced by Tolbert et al., SSCP analysis is inefficient in identifying mutations in p53. Elledge et al. discloses only limited sequencing of portions of the p53 gene from samples selected using SSCP. As such, the method of Elledge et al. will miss a significant portion of the mutations which may be present. The invention of the present claims, as amended, require the full sequencing of the entire p53 coding region from each

patient sample. One skilled in the art would not have thought to use full sequencing of the p53, given that SSCP analysis, which is much simpler, was believed to be sufficient. This is evidenced by page 60, left column, second paragraph of the Tolbert et al. article, which indicates that prior to the present invention, it was thought that SSCP analysis had a sufficiently high sensitivity for mutational analysis. However, only by sequencing the entire coding region of the p53 gene of every patient sample, will all mutations be detected. Thus, the present invention is distinguished from Elledge et al. and provides unobvious advantages over Elledge et al. Finally, contrary to the assertion of the Examiner, an advantage of an invention over a prior art reference need not be disclosed at the time of filing.

With regard to the secondary reference, there is no suggestion in Callahan of sequencing the entire p53 gene and optionally combining such sequence information with nodal status, nor is there any suggestion in Callahan of the advantages associated with such a method. As such, Callahan does not overcome the deficiencies of Elledge et al. The present invention is therefore not obvious over Elledge et al. in view of Callahan.

Claims 9-11 and 13 were further rejected as being obvious over the additional references of Hedrum et al. Applicants

believe the arguments discussed above, regarding claims 1-8 are equally applicable to the rejections of claims 9-11 and 13. In addition, the additional reference of Hedrum et al. in no way overcomes in the deficiencies of Elledge et al., Callahan and Hartmann et al. as discussed above. As such, the invention of claims 9-11 and 13 are not obvious over the cited prior art.

As the above-presented amendments and remarks address and overcome the rejections of the Examiner, withdrawal of the rejections and reconsideration and allowance of the claims are respectfully requested. Should the Examiner have any questions regarding the present application, she is requested to contact MaryAnne Liotta, PhD (Reg. No. 40,069) in the Washington DC area, at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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attachment: Talbert et al., Mod. Pathol. 12(1) 54-60 (1999)
Kressner et al., J. Clin. Oncol. 17(2) 593-599 (1999)